3. Recommendation for Exposure-Based Assessment of Joint Toxic Action of the Mixture

To conduct exposure-based assessments of possible noncancer or cancer health hazards from oral exposures to mixtures of 2,3,7,8-TCDD, hexachlorobenzene, *p,p'*-DDE, methylmercury, and PCBs, component-based approaches are recommended, because there are no direct data available to characterize health hazards (and dose-response relationships) from exposure to the mixture. In addition, PBPK/PD models have not yet been developed that would predict appropriate target doses of the components. Recommendations focus on oral exposure scenarios (e.g., from breast milk intake or other food sources) because these are most pertinent to public health concerns from these biopersistent chemicals. As discussed by ATSDR (1992, 2001a), exposure-based health assessments are used, in conjunction with evaluation of community-specific health outcome data, consideration of community health concerns, and biomedical judgement, to assess the degree of public health hazard presented by mixtures of substances released into the environment. In a component-based approach for noncancer health effects: (1) joint additive actions of the components are assumed; (2) oral intakes are calculated based on measured concentrations of the components in media of concern (e.g., breast milk); (3) intakes are divided by MRLs or target toxicity doses (TTDs); and (4) the resulting hazard quotients are summed to arrive at a hazard index. For cancer, a similar approach is taken, but the last two steps involve multiplication of the intakes by EPA cancer slope factors and summation of the resultant risk estimates.

The detection of CDDs, hexachlorobenzene, *p,p'*-DDE, methylmercury, PCBs, and other potential neurotoxicants in samples of human breast milk and maternal placental cord serum has led to epidemio-logical studies of possible neurological deficits in children exposed to persistent chemicals *in utero* and during nursing. The association reported in two epidemiological studies between frequent dietary consumption of Great Lakes fish by child-bearing-aged women and deficits in the neurological development of their children and between PCB levels in maternal body fluids and degree of neurological deficits (Fein et al. 1984; Jacobson and Jacobson 1996; Jacobson et al. 1984, 1985, 1990a, 1990b; Lonky et al. 1996; Stewart 1999, 2000b) identifies altered neurological development as a possible health hazard from frequent consumption of fish contaminated with biopersistent chemicals. Studies in North Carolina (Gladen et al. 1988; Rogan et al. 1986b), the Netherlands (Huisman et al. 1995a, 1995b; Koopman-Esseboom et al. 1996), and the Faroe Islands (Grandjean et al. 1997; 1998) have all reported associations between mild neurological deficits in children and increasing concentrations of persistent chemicals (PCBs or mercury) in maternal cord serum or breast milk samples. The observed associations, however, do not establish causal relationships between fish consumption or breast feeding and deficits in

neurological development. In contrast, there is evidence from the Dutch and Faroe Islands studies that beneficial effects of breast feeding outweigh detrimental effects that may be associated with increased exposure to biopersistent chemicals. For example, the Dutch study found an advantageous effect of breast feeding, compared with formula feeding, on fluency of movement at 18 and 42 months (Lanting et al. 1998b), and the Faroe Islands study found that early attainment of the ability to sit, creep, and stand in Faroe Island infants through 12 months of age was associated with breast feeding, which was associated with increased hair-mercury concentrations (Grandjean et al. 1995b).

Although the epidemiological studies of possible health hazards associated with exposure to biopersistent chemicals in breast milk or fish identify mild neurodevelopmental deficits as a possible health hazard, they are not directly useful for the purposes of conducting exposure-based assessments of hazards specific to a community or scenarios involving exposure to mixtures of CDDs, hexachlorobenzene, *p,p'*-DDE, methylmercury, and PCBs. In contrast, the recommended component-based approaches are useful for this purpose. There is evidence that all five components of the mixture discussed in this profile can act on the developing nervous system, and the approaches allow assessments of the possibility of altered neuro-logical development as well as other health hazards including cancer.

For exposure-based assessments of noncancer hazards from exposure to mixtures containing 2,3,7,8-TCDD, hexachlorobenzene, *p,p'*-DDE, methylmercury, and PCBs, a target-organ toxicity dose (TTD) modification of the hazard index approach as described by ATSDR (2001a) is recommended, because the components can target a wide range of overlapping health endpoints (see Table 1 in Introduction) and the critical effects (i.e., the basis of MRLs) can vary among the components depending on the component and the duration of exposure (see Table 10 in Section 2.3). For each of the components of the mixture, TTDs for chronic oral exposure scenarios have been derived as described in the Appendices, using the methods described by ATSDR (2001a). Numerical values of the TTDs (and current ATSDR chronic oral MRLs) are listed in Table 33 for the following endpoints of concern for each of the components of the mixture: hepatic, endocrine, immunological, reproductive, developmental, and neurological effects.

For the assessment of the CDDs, concentrations in the media of concern should be converted to TEQs and summed to arrive at exposure levels that can be converted to oral intakes and compared with oral MRLs

(or TTDs) for the reference dioxin, 2,3,7,8-TCDD (ATSDR 1998) or, for cancer assessment purposes (see below), used with an oral slope factor for 2,3,7,8-TCDD to estimate risk (EPA 1996; see Appendix A).

For the assessment of PCBs, concentrations of detected congeners in the media of concern should be added and converted to oral intakes (e.g., mg total PCBs/kg/day) for subsequent comparison with oral MRLs (or TTDs) for noncancer effects from PCB mixtures (ATSDR 2000) or, for cancer assessment purposes, with intakes associated with cancer risks ranging from 1×10^{-4} to 1×10^{-6}, calculated using oral slope factors derived by EPA for PCB mixtures (EPA 1996).

In the assessment of noncancer effects, hazard quotients (i.e., the ratio of an exposure estimate to the appropriate MRL) should first be calculated for each of the components (see Figure 2 in *Guidance Manual for the Assessment of Joint Toxic Action of Chemical Mixtures*, ATSDR 2001a). If two or more of the individual components have hazard quotients equaling or exceeding ratios of 0.1, then the assessment should proceed. If only one or if none of the components have a hazard quotient that equals or exceeds 0.1, then no further assessment of the joint toxic action is needed because additivity and/or interactions are unlikely to result in significant health hazard.

Table 33. Target Organ Toxicity Doses (TTDs) for Repeated Oral Exposure to Chemicals of Concern. (See Appendices A, B, C, D, and E for Details of Derivations.)

	2,3,7,8-TCDD	Hexachloro-benzene	*p,p'*-DDE	Methyl-mercury	PCBs
	Target Organ Toxicity Dose (TTD) in mg/kg/day				
Hepatic	3×10^{-9}	2×10^{-5} (chronic MRL)	7×10^{-4}	ND	1×10^{-4}
Endocrine	1×10^{-7}	1×10^{-3}	ND	ND	1×10^{-4}
Immunological	2×10^{-8}	4×10^{-4}	2×10^{-3}	3×10^{-4}	2×10^{-5} (chronic MRL)
Reproductive	1×10^{-9}	3×10^{-4}	2×10^{-3}	4×10^{-4}	2×10^{-4}
Developmental	1×10^{-9} (chronic MRL)	8×10^{-3}	2×10^{-3}	3×10^{-4} (chronic MRL)	3×10^{-5} (intermediate MRL)
Neurological	ND	8×10^{-4}	6×10^{-2}	3×10^{-4}	3×10^{-5} (intermediate MRL)

ND = not derived

Proceeding with the TTD modification of the hazard index approach involves calculating endpoint-specific hazard indices for each endpoint of concern, as described in ATSDR (2001a, Section 2.3.2 and Figure 2 with accompanying text). For example, a hazard index for developmental effects of this mixture is calculated as follows:

$$HI_{DEV} = \frac{E_{TCDD}}{MRL_{TCDD\ DEV}} + \frac{E_{HCB}}{TTD_{HCB\ DEV}} + \frac{E_{DDE}}{TTD_{DDE\ DEV}} + \frac{E_{MeHg}}{TTD_{MeHg\ DEV}} + \frac{E_{PCB}}{MRL_{PCB\ DEV}}$$

where HI_{DEV} is the hazard index for developmental toxicity, E_{TCDD} is the exposure to 2,3,7,8-TCDD (expressed in the same units as the corresponding MRL), $MRL_{TCDD\ DEV}$ is the MRL for 2,3,7,8-TCDD which is based on developmental toxicity (1×10^{-9} mg/kg/day), E_{HCB} is the exposure to hexachlorobenzene (expressed in the same units as the corresponding TDD), $TTD_{HCB\ DEV}$ is the TTD for the developmental toxicity of hexachlorobenzene, and so forth. *DDE* and *MeHg* stand for *p,p'*-DDE and methylmercury. Preliminary evidence that the exposure to the mixture may constitute a hazard is provided when the hazard index for a particular exposure scenario and health endpoint exceeds one. In practice, concern for the possibility of a health hazard increases with increasing value of the hazard index above 1.

For exposure-based assessments of cancer hazards, cancer risks are estimated by multiplying lifetime oral exposure estimates (i.e., estimated oral intakes in units of mg/kg/day) for each component by the appropriate EPA cancer oral slope factor (in units of risk per mg/kg/day). Oral cancer slope factors are available for 2,3,7,8-TCDD, hexachlorobenzene, *p,p'*-DDE, and PCBs (see Appendices A, B, C, and E). If two or more of the components have cancer risks equal to or exceeding 1×10^{-6}, then the component cancer risks are summed to derive a cancer risk estimate for the mixture. If only one or if none of the component risks equals or exceeds 1×10^{-6}, then no further assessment of joint toxic action is needed due to the low likelihood that additivity and/or interactions would result in a significant health hazard. Mixture cancer risks equaling or exceeding 1×10^{-4} are taken as an indicator that the mixture may constitute a health hazard.

The addition of hazard quotients (or cancer risks) for a particular exposure scenario assumes that the mixture components additively act on a common toxicity target by a common mechanism or mode of action, and that less-than-additive (e.g., antagonistic interactions) or greater-than-additive (e.g., synergism or potentiation) interactions do not occur among the components of the mixture. A primary objective of this profile is to assess available information on modes of joint toxic actions of 2,3,7,8-TCDD, hexa-

chlorobenzene, *p,p'*-DDE, methylmercury, and PCBs. As discussed in Section 2.3, a weight-of-evidence approach was used to evaluate the possible influence of binary interactions among the components in the overall toxicity of the mixture. Table 32 (at the end of Section 2.3) lists BINWOE determinations that were made for the joint action on various endpoints by the 10 pairs of the components. There is only a limited amount of evidence that interactions exist between a few of the chemical pairs:

C   hexachlorobenzene potentiation of TCDD reduction of body and thymus weights;

C   PCB antagonism of TCDD immunotoxicity and developmental toxicity; and

C   synergism between PCBs and methylmercury in disrupting neurological function and development.

The low BINWOE numerical scores for these possible interactions (none are higher than 0.2 compared with a maximum score of 1) reflect the quality of the data on which they are based and indicate a fair amount of uncertainty that they will occur (Table 32). For the remaining pairs, additive joint action at shared targets of toxicity is either supported by data (for a few pairs) or is recommended as a public health protective assumption due to lack of interaction data, conflicting interaction data, and/or lack of mechanistic understanding to reliably support projections of modes of joint toxic action (Table 32). The weight-of-evidence analysis indicates that scientific evidence that greater-than-additive or less-than-additive interactions will occur among the five components is limited and supports the use of the additivity assumption as a public health protective measure in exposure-based assessments of health hazards from exposure to mixtures of CDDs, hexachlorobenzene, *p,p'*-DDE, methylmercury, and PCBs.